

FGFR1 amplifications in squamous cell carcinomas of the lung: diagnostic and therapeutic implications

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Abstract: Fibroblast growth factor receptor 1 (FGFR1) is a type 4 receptor tyrosine kinase. The receptor and its ligands play an important role in development and physiology. However, constitutive activation of FGFR1 by gene amplification, translocation or mutation is associated with various malignancies as, for example, breast cancer or myeloproliferative diseases. We have recently reported that *FGFR1* amplification occurs in 20% of pulmonary squamous cell carcinomas, and preclinical tests have shown that these alterations are therapeutically tractable. These findings make *FGFR1* amplification a potential biomarker for lung cancer treatment.

Squamous cell carcinomas of the lung are characterized by an uneven *FGFR1* gene copy number distribution. Therefore, fluorescence in situ hybridization assays need to address focality and heterogeneity of *FGFR1* in these tumors. Here, we review our proposal for a reading and evaluation strategy. Furthermore, we highlight the emerging landscape of clinical trials with selective and unselective FGFR inhibitors and provide first response data from early clinical trials.

Key Words: Lung cancer; squamous cell carcinoma; *fibroblast growth factor receptor 1 (FGFR1)*; FISH



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Introduction

Fibroblast growth factor receptor 1 (FGFR1) amplification represents now one of the most promising predictive biomarkers in lung cancer. This alteration seems to become the first therapeutically relevant genetic change in pulmonary squamous cell carcinomas, which occurs frequently in these tumors. In contrast to adenocarcinomas of the lung, squamous cell carcinomas do not significantly harbor *EGFR* mutations or *ALK*, *ROS1* or *RET* translocations, which are therapeutically tractable. Therefore, *FGFR1* amplifications in pulmonary squamous cell carcinomas are currently in the focus of many researchers and various ongoing clinical trials.

Squamous cell carcinoma is a common subgroup of lung cancer, which is strongly associated with smoking. The

estimated annual incidence is approximately 123 newly diagnosed cases per 100,000 inhabitants in Europe (1,2). It is suspected that both incidence and prevalence will still increase, especially among female patients. The current therapeutic regimen for locally advanced or metastatic tumors consists of conventional platinum based chemotherapy and radiation (3). Very recently, data from our group indicated, however, that a focal amplification of chromosome band 8p12, representing the second most common genetic alteration, occurs in pulmonary squamous cell carcinomas which was proven to be related to *FGFR1* amplification (4). Subsequently, we could confirm this finding in a large cohort of 420 clinical lung cancer samples by fluorescence in situ hybridization (5). Furthermore, data from *in vitro* studies provided first evidence that *FGFR1*

amplified squamous cell lines are in fact exploitable by FGFR inhibitors (4).

The FGFR family of receptor tyrosine kinases

FGFR1 is a member of the type 4 family of receptor tyrosine kinases, which consists of the closely related and highly conserved FGFRs 1 to 4. All these proteins are transmembrane receptors which are composed of an extracellular ligand binding domain, a transmembrane domain and an intracellular part which contains the functionally relevant tyrosine kinase domain. Three immunoglobulin-like loops (IgI-III) build the extracellular part, with IgI and II being separated by a so-called acid box of few amino acid residues. IgII and III form the ligand binding site. The binding specificity of the receptors is regulated by alternative splicing of the IgIII portion as exons 8 and 9 build alternatively the C-terminal part of this domain, thus forming the IIIb or IIIc variant of the receptor, respectively (6). Epithelial tissues express mostly the IIIb variant, whereas IIIc predominates in mesenchymal cells (7). This alternative splicing is, however, restricted to *FGFR1-3* with *FGFR4* being expressed always in the IIIc form.

FGFRs are activated by binding of their specific ligands - the fibroblast growth factors (FGFs) of which 18 different types are currently known. FGFs can function in an autocrine or paracrine manner and may even have hormonal long-distance effects. Furthermore, FGFs can also be liberated from the stroma, for instance during invasive tumor growth. FGFs bind with high specificity to FGFRs and form a complex with dimerized receptor molecules and a heparan sulphate proteoglycan chain. These activated complexes undergo conformation change and activation of the tyrosine kinase domains which finally trans-phosphorylate. After binding and phosphorylation of adapter proteins FGF signaling functions via different downstream effectors, e.g., the signal transducer and activator of transcription (STAT) pathway. Another signaling axis consists of phospholipase C γ , protein kinase C and ends in the RAS - MAP kinase pathway. An important regulator of FGFR signaling is FGFR substrate 2 (FRS2) which binds to the juxtamembrane domain of activated FGF receptors and which recruits GRB2 and other downstream molecules finally leading again to an activation of the RAS - RAF - MAP kinase pathway as well as the PI3K - AKT pathway. Among others proteins FGFR-like 1 (FGFRL1 or FGFR5) functions as a negative regulator. FGFRL1 has the capability of binding (or "trapping") FGFs

without subsequent tyrosine kinase activity.

FGFR activity and FGF signaling play a major role in development, proliferation, differentiation and survival. Thus, FGFRs are crucial for embryogenesis, e.g., for limb development and organogenesis, and are highly important for many physiological processes including wound healing. In this context, FGFRs can act even as tumor suppressors.

The role of *FGFR1* in oncogenesis

Gains of function of the FGF receptors were found to be associated with various malignancies. Constitutive activation of FGFR1 occurs basically by three major mechanisms: gene amplification, translocation or activating mutations (for overview and selected references see *Table 1*). *FGFR1* mutations have been reported in melanomas but this appears to be a rather rare event. *FGFR1* amplification, however, belongs to the most frequent genetic changes in breast cancer. Amplification of *FGFR1* has additionally been reported in squamous cell carcinomas of the head and neck as well as from the esophagus. Translocations of *FGFR1* have originally been described in a myeloproliferative hematological disorder which has now been referred to as "8p11 myeloproliferative syndrome characterized by *FGFR1* translocation" by the current WHO classification system. Very recently *FGFR1* translocations were additionally found in a subset of glioblastoma multiforme and in a rhabdomyosarcoma.

Altered FGF receptor activity contributes to cancer development by regulating different key processes. Meanwhile, there is clear evidence that unscheduled FGFR activation leads to an increase in cell proliferation and prolonged survival but also cell migration and angiogenesis are stimulated.

FGFR1 amplification in lung cancer - epidemiology

Very recently we have reported on the frequency of *FGFR1* amplifications in pulmonary carcinomas. In the so far largest series we found 20% *FGFR1* amplified tumors among squamous cell carcinomas (5) which was recently confirmed in a second independent study (19). Therefore, *FGFR1* amplification represents one of the most frequent driver lesions in lung cancer next to *EGFR* mutations, and far more often than *ALK*, *ROS1* or *RET* rearrangements or other therapeutically targetable alterations. The high frequency as well as the large list of potential inhibitors which are currently in early or advanced clinical trials make

Table 1 *FGFR1* alterations in malignancies

<i>FGFR1</i> alterations	Tumor entities (estimated frequency)	Selected references
Amplification	Breast cancer (10%)	Reis-Filho <i>et al.</i> [2006] (8)
	Ovarian cancer (5%)	Gorringe <i>et al.</i> [2007] (9)
	Bladder cancer (3%)	Simon <i>et al.</i> [2001] (10)
	Rhabdomyosarcoma (3%)	Missiaglia <i>et al.</i> [2009] (11)
	Squamous cell carcinoma of the lung (20%)	Schildhaus <i>et al.</i> [2012] (5)
	Small cell carcinoma of the lung (5%)	Peifer <i>et al.</i> [2012] (12)
	Head and neck squamous cell carcinomas (17%)	Freier <i>et al.</i> [2007] (13)
	Esophageal squamous cell carcinoma	Randla <i>et al.</i> [2012] (14)
Translocation	8p11 myeloproliferative syndrome [<i>ZNF198-FGFR1</i>] (100%, entity defining alteration as part of myeloid and lymphoid neoplasms with abnormalities of <i>FGFR1</i> and various translocation partners of <i>FGFR1</i>)	WHO classification [2008] (15)
	Chronic myeloid leukemia (rare)	WHO classification [2008] (15)
	Rhabdomyosarcoma [<i>FOXO1-FGFR1</i>] (one case)	Liu <i>et al.</i> [2011] (16)
	Glioblastoma multiforme [<i>TACC-FGFR1/3</i>] (3%)	Singh <i>et al.</i> [2012] (17)
Activating mutation	Melanoma (rare)	Lin <i>et al.</i> [2008] (18)

FGFR1 amplification one of the most promising biomarkers for lung cancer treatment.

It is, however, noteworthy that - at least until now - no convincing case of an adenocarcinoma has been proven to be *FGFR1* amplified. In our series of nearly one hundred pulmonary adenocarcinomas all cases were clearly negative for gene amplifications whereas polysomic cases were frequently noticed (5). This finding seems to be restricted to pure adenocarcinomas as we have seen *FGFR1* amplification occasionally in adeno-squamous carcinomas. Furthermore, we have found additionally a pulmonary large cell carcinoma *FGFR1* amplified (5). This might reflect the fact that emerging data from expression profiles provide evidence that some pulmonary large cell carcinomas represent a dedifferentiation endpoint of squamous carcinomas. Taken together, among non small cell carcinomas, *FGFR1* amplification seems to be strongly associated with squamous morphology.

Very recently, we further reported that also small cell carcinomas of the lung can harbor *FGFR1* amplifications (12). Preliminary and not yet published data from our screening program provide first evidence that this is a reproducible finding which can be confirmed in clinical routine cohorts. The frequency of *FGFR1* amplifications among small cell carcinomas seems to be lower than in squamous cell carcinomas. Based on our current and still ongoing epidemiologic studies we estimate the frequency of *FGFR1* amplifications among small cell carcinomas around 5%.

Detection of *FGFR1* amplifications by fluorescence in situ hybridization

Therapeutic effects of *FGFR1* tyrosine kinase inhibitors seem to be dependent on significantly increased *FGFR1* gene copy numbers. It still needs to be clarified whether *FGFR1* amplification only serves as a surrogate marker for receptor protein overexpression since the receptor itself should represent obviously the therapeutic target. There are currently no validated antibody assays on the market, which could reliably detect *FGFR1* expression levels quantitatively or semiquantitatively by using paraffin embedded tumor samples. Thus, comprehensive studies on the correlation between *FGFR1* gene copy numbers and protein expression levels are still missing. Therefore, current clinical trials with *FGFR1* inhibitors enroll patients who are found to be “*FGFR1* amplified”. Reliable *FGFR1* FISH probes are now commercially available. Therefore, fluorescence in situ hybridization assays on formalin fixed and paraffin embedded material are carried out to screen patients for clinical trials. This is an important fact as lung cancer samples *per se* are often hard to diagnose. Biopsy samples, which are obtained endoscopically or by transthoracic CT-guided biopsy are often very small and contain only little tumor tissue. Tumor cells are frequently damaged by manipulations and show often crushing artifacts. Surgical samples contain often large tumor areas of necrosis or dense fibrosis which regularly influence hybridization quality.

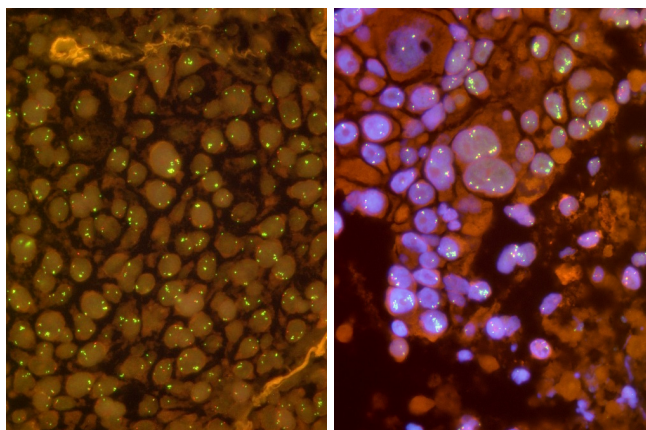


Figure 1 Fluorescence in situ hybridization for detection of *FGFR1* amplification in pulmonary squamous cell carcinomas. A. In this tumor, *FGFR1* (green) and chromosome 8 (CEN8, orange) copies are more or less evenly distributed. Only occasionally, microclusters are seen (arrow); B. Heterogeneity occurs frequently in these tumors. Beside tumor cells with normal or only slight increase in copy numbers, there are many tumor cell nuclei with tight clusters of amplified *FGFR1*, some of which are indicated by arrows. Note that the occurrence of *FGFR1* clusters is not necessarily related to the size of the nuclei

Therefore, lung cancer tissue is basically a challenge for FISH. Despite this fact we were able to establish a robust and reliable FISH assay, and we have noticed a drop out rate below 5% in our laboratory by using our protocol (5).

FGFR1 amplification is not yet convincingly defined. Some authors have simply applied the criteria which are commonly used for detection of *her2* amplifications in breast cancer. From our experience, however, these criteria are not useful to evaluate *FGFR1* FISH assays for squamous cell carcinomas of the lung. *FGFR1* in these tumors is characterized by some unique features which make *FGFR1* FISH assays challenging. One major issue is heterogeneity and focality of gene amplifications (Figure 1). Thus, adequate screening for amplification hot spots is a prerequisite for reliable *FGFR1* evaluation. Based on our reading and evaluation strategy (5), we recommend careful scanning of the entire tumor area by using a 40× or 63× oil objective. *FGFR1* and centromere 8 (CEN8) signals should be counted for individual tumor cells (63× or 100× oil objective). We suggest counting of 20 tumor cell from three areas, resulting in a total of 60 nuclei. Counting areas should be selected from prior screening as the hot spot areas containing the highest number of *FGFR1* copies. If

the signals are found to be evenly distributed random areas should be used. Another important phenomenon is focality of *FGFR1* gene copy distribution. Very often isolated tumor cells with a very high number of *FGFR1* gene copies occur which are surrounded by tumor cells with normal or only slightly increased gene copy numbers. Therefore, it turned out to be mandatory to count contiguous and cohesive tumor cells from each area. It should be avoided to pick only suspicious tumor cell nuclei with increased *FGFR1* and/or CEN8 copy numbers because this approach might lead to an overestimation of gene copy numbers.

Furthermore, the gene copy distribution in pulmonary squamous cell carcinomas is different from e.g., *her2* in breast cancer. A significant proportion of tumors show colocalized clusters with numerically balanced increase in both *FGFR1* and CEN8 copy numbers. Another more or less specific feature represents so-called microclusters which consist of a tight accumulation of more than three *FGFR1* signals. We have proposed to regard these microclusters as 5 signal copies.

Having counted 60 tumor cells a final decision has to be made whether a given sample is “amplified” or not. As already mentioned there are until now no convincing criteria to judge *FGFR1* FISH assays in squamous cell carcinomas. From our point of view this FISH assay should finally serve as a predictive biomarker which should be capable to predict response to anti-FGFR treatment. However, criteria for thresholds and cut-off values still have to be determined retrospectively after finishing the currently ongoing clinical trials individually for each compound. Therefore, we have developed evaluation criteria (“Cologne Score”) which are suitable to detect patients with the highest gene copy numbers and to enroll them in clinical trials. In this context, it seems to be important to us not only to use *FGFR1*/CEN8 ratio as criterion for FISH positivity since we have noticed tumors with an enormous increase in *FGFR1* gene copy numbers in a background of co-localized clusters, i.e. an additional increase of centromeric DNA material. These cases would finally result in a ratio of nearly 1.0 and would be considered negative if the decision would rest solely on *FGFR1*/CEN8 ratio. Therefore, it appears useful also to consider average gene copy number as a criterion for positivity. Furthermore, we have seen isolated tumor cells with high level cluster amplification which were surrounded by lesional cells with normal or only slightly increased gene copy numbers. Thus, we proposed to include additionally the percentage of tumor cell with gene clusters of at least 15 gene copies in the catalogue of FISH criteria.

Considering all these items we have proposed to diagnose *FGFR1* amplification (“high level amplification”) if one of the following criteria is fulfilled: (I) *FGFR1/CEN8* ratio is ≥ 2.0 , (II) average gene copy per nucleus is ≥ 6.0 , and (III) percentage of tumor cells containing ≥ 15 gene copies or large cluster is $\geq 10\%$.

Beside unamplified tumors with nearly normal gene count and amplified cases as defined above we became aware of a third category of squamous cell carcinomas which is characterized by a moderate increase of *FGFR1* gene copies. For these more or less polysomic cases we have defined a “low level amplification” category which we defined by a percentage of $\geq 50\%$ of tumor cells containing ≥ 5 *FGFR1* gene copies. This criterion was derived and adapted from previous studies on squamous cell carcinomas of the head and neck as well as from reports on breast cancer (8,13). Since polysomy is a common phenomenon in cancer, one might expect that many squamous cell lung cancers might fall into this category. It is, however, important to emphasize the fact that this low level amplification contributes for only one fifth of the amplified pulmonary squamous carcinomas. Low level amplification is found in only 4% of these tumors.

Therapeutic implications resulting from oncogenic FGFR dependence

The identification of FGFR alteration in various types of human cancer led to rapid development of compounds targeting FGFR. As described above, the FGFR family comprises 4 members (*FGFR1*, 2, 3 and 4). The small molecules act either as selective pan inhibitors of the FGFR family or as non-selective inhibitors, which usually target not only FGFR but also other intracellular proteins. *Table 2* summarizes FGFR inhibitors in current clinical development.

Currently ongoing phase Ia/Ib and phase II studies recruit patients either with diagnosed *FGFR* alterations only or include unselected patient populations [for overview of FGFR trials see ref (20)].

The phase I/II studies with AZD4547, BGJ398, E-3810 and dovitinib include only patients with genetic *FGFR* alterations. The phase II with ponatinib is recruiting patients with squamous cell carcinoma with retrospective outcome analysis of *FGFR* altered patients (20).

Nintedanib and XL999 were investigated in advanced non small cell lung cancer (NSCLC) without further selection (1,21). All other trials recruited patients with different solid tumors without any further molecular analysis.

Trials recruiting patients with FGFR alterations

BGJ398 is a selective FGFR inhibitor which blocks *FGFR1*, *FGFR2* and *FGFR3*. The drug is supposed to be effective in tumors with activated FGFR axis due to activating mutations or gene amplification. The BGJ398 phase Ia (first in man) trial recruited patients with solid tumors in an escalating dose schedule starting from 5 mg daily. After cohort 3, only patients with *FGFR1* or *FGFR2* amplification or *FGFR3* mutation are included. Preliminary analysis was conducted after 26 recruited patients including 10 patients with *FGFR1* amplified breast cancer and 3 patients with *FGFR1* amplified squamous cell carcinomas of the lung. One patient with *FGFR1* amplified squamous cell lung cancer with an *FGFR1/CEP8* ratio of 2.6 by FISH analysis treated with 100 mg BGJ398 showed partial response in CT scan at 8 weeks, confirmed at 12 weeks with a substantial SUV decrease on PET scan at week 4 (22). The trial is currently treating patients with *FGFR* alterations on maximal tolerated dose in the expansion part of the phase I.

The phase I study with the selective FGFR inhibitor AZD4547 (*FGFR* 1, 2, 3 inhibitor) is currently recruiting patients with *FGFR* amplified tumors at a maximal tolerated dose.

Dovitinib - as an unselective FGFR inhibitor - blocks also VEGFR 1, 2, 3 and PDGFR β besides *FGFR* 1, 2, 3. First phase I/II studies were conducted in patients with metastatic melanoma without any pre-selection according to genetic alterations. A moderate clinical benefit of stable disease was reached in 12 from 47 enrolled patients (23). The phase I/II study in patients with advanced or metastatic renal cell cancer showed 2 partial responses from 20 recruited patients (24). A phase II study treating 77 metastatic breast cancer patients showed 13% partial responses in the group of patients who were *FGFR1* amplified and hormone positive (25). Phase II studies in patients with metastatic gastric cancer and *FGFR2* amplification and in patients with advanced endometrium cancer and *FGFR2* mutation (stratified to non-mutated patients) are currently ongoing (20).

The expansion part of the phase I study with E-3810, a combined inhibitor of *FGFR* 1 and VEGFR 1, 2, 3, is recruiting patients with *FGFR1* amplification and patients relapsing after response or long stable disease after anti-angiogenic treatment (26).

Ponatinib is a multikinase inhibitor of *FGFR*-1, 2, 3, 4, Abl, Src, FLT-3 and c-KIT showing high clinical activity in heavily pretreated patients with chronic myeloid leukemia resistant

Table 2 Selective and non-selective FGFR inhibitors in current clinical development

FGFR inhibition	Drugs	Receptor targets	Provider
Selective	AZD4547	FGFR 1, 2, 3	Astra Zeneca
	BGJ398	FGFR 1, 2, 3	Novartis
	JNJ-42756493	pan FGFR	Janssen Research & Development
Non-selective	ARQ087	pan FGFR	ArQuele
	Brivanib	FGFR 1	Bristol-Meyers-Squibb
		VEGFR 2	
	Danusertib	FGFR 1	Nerviano Medical Sciences
		Aurora kinase A, B, C	
	Dovitinib	Abl, Ret, TrkA	Novartis
		FGFR 1, 2, 3	
	E-3810	VEGFR 1, 2, 3	Ethical Oncology Science (EOS)
		FGFR 1	
	FP-1039	FGF ligand trap	Five Prime Therapeutics
	LY2874455	FGFR 1, 2, 3, 4	Eli Lilly
		VEGFR 2	
	MK-2461	FGFR 1, 2, 3	Chemfun Medical technology
		c-Met, Ron	
		Flt-1, 3, Mer	
Nintedanib	PDGFR β	BoehringerIngelheim	
	FGFR 1, 2, 3		
	VEGFR 1, 2, 3		
Orantinib	PDGFR α/β	TaihoPharmaceutical Co., Ltd.	
	FGFR 1		
	VEGFR 2		
Ponatinib	FGFR 1, 2, 3, 4	Ariad Pharmaceuticals	
	Abl, Src		
	FLT-3, c-KIT		
XL228	FGFR 1	Exelixis	
	IGF1R		
	Aurora A, B		
	FAK, Src		
XL999	BCR-Abl	Exelixis	
	FGFR 1, 3		
	VEGFR 2		
	PDGFR α/β		
		FLT-3, Src	

to other tyrosine kinase inhibitors (27). The phase II study enrolling squamous cell lung cancer patients with retrospective analysis of FGFR alterations is currently ongoing (20).

Trials recruiting NSCLC patients without molecular testing

Nintedanib, a FGFR 1, 2, 3, VEGFR 1, 2, 3 and PDGFR α/β inhibitor showed clinical activity in phase I in advanced solid tumors with one complete and two partial responses occurred in patients with renal (n=2) and colorectal cancer (n=1) among 61 recruited patients (28). The phase II study in unselected patient population with NSCLC showed one partial response and 35 stable diseases in 73 treated patients (21).

XL999 is a multikinase inhibitor of FGFR 1, 3, VEGFR 2, PDGFR α/β , FLT-3 and Src. The preliminary results of a phase II study in nine NSCLC patients showed one partial response (29).

Trials recruiting other cancer entities without molecular testing

Brivanib (FGFR 1 and VEGFR 2 inhibitor) is one of the few FGFR compounds in late clinical development. The phase I was performed in an unselected patient population. In a dose finding part, the best response was stable disease in 1 patient with NSCLC from 5 patients with different tumor entities (30). Another large phase I study recruited 68 patients with different tumor entities. Two patients achieved partial response, one with renal cell carcinoma and one with a carcinoma of Vater's ampulla (31). The phase II study on brivanib in 55 patients with hepatocellular carcinoma (HCC) showed one complete and 3 partial responses. The median progression free survival (PFS) and overall survival (OS) were 2.7 and 10 months, respectively (32).

In the phase II discontinuation trial, patients with various tumors and stable disease after initial treatment with brivanib was stratified according to FGF-2 expression and randomized to receive either brivanib or placebo. Fifty-three patients with FGF-2 expression and soft tissue sarcoma showed a PFS of 2.8 months in a brivanib group comparing to 1.4 months in the placebo group (33). Regarding the phase III trials, the study in patients with HCC after failure on sorafenib did not meet its primary endpoint in improving of OS (34).

Phase I study with JNJ-42756493, a selective pan FGFR inhibitor is currently ongoing in an unselected patient population with solid tumors and lymphomas after standard

treatment (20). Similarly, phase I study with ARQ087 recruiting unselected patients with solid tumors is currently ongoing (20).

The phase I study with danusertib, which inhibits besides FGFR 1 also Aurora kinase A, B, C, Abl, Ret and TrkA was performed in unselected patient population. Although the compound showed some clinical benefit in small cell lung, colorectal, breast and ovarian cancer, the adverse effect were characterized due to pronounced hematological toxicity with febrile neutropenia (35). The phase II study on danusertib in metastatic castration resistant prostate cancer showed moderate clinical activity with median PFS of 3 months (36).

FP-1039 is a ligand trap, which binds to FGF ligands and prevents them from binding to FGFRs. A phase I study recruiting patients with all solid tumors showed moderate clinical activity with tumor shrinkage of 20% in a patient with a prostate cancer (37). Phase II study enrolling patients with *FGFR2* mutated endometrial cancer is currently ongoing (20).

LY2874455 is an inhibitor of all FGF receptors with low VEGFR 2 activity (38). The phase I study recruiting patients with all types of advanced cancer (20).

MK-2461 is a common inhibitor of FGFR 1, 2, 3, c-Met, Ron, Flt-1, 3 and PDGFR β . The phase I in solid tumors showed mild clinical activity (39).

Orantinib, a multikinase inhibitor of FGFR 1, VEGFR 2 and PDGFR β was investigated mainly in hepatocellular carcinoma (HCC). A phase I/II study in 35 patients with HCC showed one complete and two partial responses (40).

XL228 is a multikinase inhibitor of *FGFR1*, IGF1R, Aurora A, B, FAK, Src and bcr-abl. The phase I study in advanced solid tumors and lymphoma showed one partial response in a patient with adenocarcinoma of the lung (41).

Conclusions

A great variety of FGFR inhibitors is currently in clinical development. First results show that these drugs basically have therapeutic effects on solid and hematologic tumors. Data from trials enrolling lung cancer patients indicate that genetic prescreening increases antitumoral efficacy since we could provide first evidence for therapeutic response of a pulmonary *FGFR1* amplified squamous cell carcinoma patient to treatment with a selective FGFR inhibitor. Therefore, FISH is currently the method of choice to detect squamous cell carcinomas of the lung with *FGFR1* amplification.

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